| | Type | L # | Hits | Search Text | DBs | Time Stamp | Comments | Error Definition | Errors |
|---|---|---|---|---|---|---|---|---|---|
| 1 | BRS | L1 | 17475 | macrophage | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2002/01/31 15:28 | | | 0 |
| 2 | BRS | L2 | 11385 | glutathione or GSH | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2002/01/31 15:29 | | | 0 |
| 3 | BRS | L3 | 139 | 1 same 2 | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2002/01/31 15:29 | | | 0 |
| 4 | BRS | L4 | 2909 | cachectic or cachexia | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2002/01/31 15:29 | | | 0 |
| 5 | BRS | L5 | 132317 | cancer or diabetes or (gastrointestinal adj inflammatory adj disease) or (chronic adj rheumatoid adj arthritis) or hepatitis or (hepatic adj cirrhosis) or (hypersensitive adj interstitial adj pneumonia) or (pulmonary adj fibrosis) or (autoimmune adj inflammatory adj disease) | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2002/01/31 15:30 | | | 0 |

| | Type | L # | Hits | Search Text | DBs | Time Stamp | Comments | Error Definition | Errors |
|---|---|---|---|---|---|---|---|---|---|
| 6 | BRS | L6 | 1825 | (cachectic or cachexia) same (cancer or diabetes or (gastrointestinal adj inflammatory adj disease) or (chronic adj rheumatoid adj arthritis) or hepatitis or (hepatic adj cirrhosis) or (hypersensitive adj interstitial adj pneumonia) or (pulmonary adj fibrosis) or (autoimmune adj inflammatory adj disease)) | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2002/01/31 15:31 | | | 0 |
| 7 | BRS | L7 | 7134 | cystine | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2002/01/31 15:31 | | | 0 |

| | Type | L # | Hits | Search Text | DBs | Time Stamp | Comments | Error Definition | Errors |
|---|---|---|---|---|---|---|---|---|---|
| 8 | BRS | L8 | 3 | ((cachectic or cachexia) same (cancer or diabetes or (gastrointestinal adj inflammatory adj disease) or (chronic adj rheumatoid adj arthritis) or hepatitis or (hepatic adj cirrhosis) or (hypersensitive adj interstitial adj pneumonia) or (pulmonary adj fibrosis) or (autoimmune adj inflammatory adj disease))) same cystine | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2002/01/31 15:32 | | | 0 |
| 9 | BRS | L9 | 58 | (cancer or diabetes or (gastrointestinal adj inflammatory adj disease) or (chronic adj rheumatoid adj arthritis) or hepatitis or (hepatic adj cirrhosis) or (hypersensitive adj interstitial adj pneumonia) or (pulmonary adj fibrosis) or (autoimmune adj inflammatory adj disease)) same cystine | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2002/01/31 15:33 | | | 0 |

| | Type | L # | Hits | Search Text | DBs | Time Stamp | Comments | Error Definition | Errors |
|---|---|---|---|---|---|---|---|---|---|
| 10 | BRS | L10 | 0 | ((cachectic or cachexia) same (cancer or diabetes or (gastrointestinal adj inflammatory adj disease) or (chronic adj rheumatoid adj arthritis) or hepatitis or (hepatic adj cirrhosis) or (hypersensitive adj interstitial adj pneumonia) or (pulmonary adj fibrosis) or (autoimmune adj inflammatory adj disease))) same cystine same 3 | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2002/01/31 15:34 | | | 0 |

| | Type | L # | Hits | Search Text | DBs | Time Stamp | Comments | Error Definition | Errors |
|---|---|---|---|---|---|---|---|---|---|
| 11 | BRS | L11 | 58 | (cancer or diabetes or (gastrointestinal adj inflammatory adj disease) or (chronic adj rheumatoid adj arthritis) or hepatitis or (hepatic adj cirrhosis) or (hypersensitive adj interstitial adj pneumonia) or (pulmonary adj fibrosis) or (autoimmune adj inflammatory adj disease)) same cystine | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2002/01/31 15:33 | | | 0 |
| 12 | BRS | L12 | 2 | (cancer or diabetes or (gastrointestinal adj inflammatory adj disease) or (chronic adj rheumatoid adj arthritis) or hepatitis or (hepatic adj cirrhosis) or (hypersensitive adj interstitial adj pneumonia) or (pulmonary adj fibrosis) or (autoimmune adj inflammatory adj disease)) same cystine same 3 | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2002/01/31 15:33 | | | 0 |

| | Type | L # | Hits | Search Text | DBs | Time Stamp | Comments | Error Definition | Errors |
|---|---|---|---|---|---|---|---|---|---|
| 13 | BRS | L14 | 2 | ((cachectic or cachexia) same (cancer or diabetes or (gastrointestinal adj inflammatory adj disease) or (chronic adj rheumatoid adj arthritis) or hepatitis or (hepatic adj cirrhosis) or (hypersensitive adj interstitial adj pneumonia) or (pulmonary adj fibrosis) or (autoimmune adj inflammatory adj disease))) same 3 | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2002/01/31 15:34 | | | 0 |
| 14 | BRS | L13 | 18 | (cancer or diabetes or (gastrointestinal adj inflammatory adj disease) or (chronic adj rheumatoid adj arthritis) or hepatitis or (hepatic adj cirrhosis) or (hypersensitive adj interstitial adj pneumonia) or (pulmonary adj fibrosis) or (autoimmune adj inflammatory adj disease)) same 3 | USPAT; US-PGPUB; EPO; JPO; DERWENT | 2002/01/31 15:34 | | | 0 |

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(FILE 'HOME' ENTERED AT 14:53:22 ON 31 JAN 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, AGRICOLA' ENTERED AT 14:53:49 ON
31 JAN 2002
L1 448179 S MACROPHAGE
L2 225702 S GLUTATHIONE OR GSH
L3 2653 S L1 (P) L2
L4 44743 S CYSTINE
L5 95 S L3 (P) L4
L6 1789 S CACHECTIC OR CHACHEXIA
L7 2386695 S CANCER OR DIABETES OR (GASTROINTESTINAL INFLAMMATORY DISEASE)
L8 792 S L6 AND L7
L9 1 S L5 AND L8
L10 2 S L3 AND L8
L11 1 S L10 NOT L9
L12 164 S (L3 OR L5 ) AND L7
L13 7 S L12 AND L4
L14 4 DUPLICATE REMOVE L13 (3 DUPLICATES REMOVED)
L15 3 S L14 NOT L10

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FILE 'HOME' ENTERED AT 14:53:22 ON 31 JAN 2002

=> file medline caplus biosis embase agricola

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 0.15 | 0.15 |

FILE 'MEDLINE' ENTERED AT 14:53:49 ON 31 JAN 2002

FILE 'CAPLUS' ENTERED AT 14:53:49 ON 31 JAN 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.


FILE 'BIOSIS' ENTERED AT 14:53:49 ON 31 JAN 2002


FILE 'EMBASE' ENTERED AT 14:53:49 ON 31 JAN 2002


FILE 'AGRICOLA' ENTERED AT 14:53:49 ON 31 JAN 2002

=> s macrophage
L1 448179 MACROPHAGE

=> s glutathione or GSH
L2 225702 GLUTATHIONE OR GSH

=> s l1 (p) l2
L3 2653 L1 (P) L2

=> s cystine
L4 44743 CYSTINE

=> s l3 (p) l4
L5 95 L3 (P) L4

=> s cachectic or chachexia
L6 1789 CACHECTIC OR CHACHEXIA

=> s cancer or diabetes or (gastrointestinal inflammatory disease) or (chronic rheumatoid arthritis) or (hepatitis or (hepatic cirrhosis) or (hypersensitive interstitial pneumonia) or (pulmonary fibrosis) or (autoimmune inflammatory disease)
UNMATCHED LEFT PARENTHESIS 'OR (HEPATITIS'
The number of right parentheses in a query must be equal to the number of left parentheses.

=> s cancer or diabetes or (gastrointestinal inflammatory disease) or (chronic rheumatoid arthritis) or hepatitis or (hepatic cirrhosis) or (hypersensitive interstitial pneumonia) or (pulmonary fibrosis) or (autoimmune inflammatory disease)
2 FILES SEARCHED...
3 FILES SEARCHED...
L7 2386695 CANCER OR DIABETES OR (GASTROINTESTINAL INFLAMMATORY DISEASE) OR (CHRONIC RHEUMATOID ARTHRITIS) OR HEPATITIS OR (HEPATIC CIRRH

CEP-HTM

OSIS) OR (HYPERSENSITIVE INTERSTITIAL PNEUMONIA) OR (PULMONARY FIBROSIS) OR (AUTOIMMUNE INFLAMMATORY DISEASE)

=> s l6 and l7
L8 792 L6 AND L7

=> s l5 and l8
L9 1 L5 AND L8

=> d l9 1 ibib abs

L9 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:161498 CAPLUS
DOCUMENT NUMBER: 134:202694
TITLE: Method using a **cystine** derivative for suppressing immune responses and treating **cachectic** conditions by reducing intracellular content of **glutathione** in **macrophages** and monocytes
INVENTOR(S): Hamuro, Junji; Murata, Yukie
PATENT ASSIGNEE(S): Ajinomoto Co., Inc., Japan
SOURCE: U.S., 26 pp., Cont.-in-part of U.S. Ser. No. 181,881.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6197749 | B1 | 20010306 | US 1999-334647 | 19990617 |
| US 2001000784 | A1 | 20010503 | US 2000-731830 | 20001208 |

PRIORITY APPLN. INFO.: US 1998-181881 A2 19981029
JP 1997-312727 A 19971029
JP 1998-308300 A 19981029
US 1999-334647 A1 19990617

OTHER SOURCE(S): MARPAT 134:202694
AB A method of suppressing immune responses comprises administering to a patient in need thereof an effective amt. of a compn. comprising a substance capable of reducing the content of reductive **glutathione** in **macrophages**. Compds. of the invention include **cystine** derivs. A method for treating **cachectic** conditions is also disclosed.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

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(FILE 'HOME' ENTERED AT 14:53:22 ON 31 JAN 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, AGRICOLA' ENTERED AT 14:53:49 ON 31 JAN 2002
L1 448179 S MACROPHAGE
L2 225702 S GLUTATHIONE OR GSH
L3 2653 S L1 (P) L2

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L4        44743 S CYSTINE
L5           95 S L3 (P) L4
L6         1789 S CACHECTIC OR CHACHEXIA
L7      2386695 S CANCER OR DIABETES OR (GASTROINTESTINAL INFLAMMATORY
DISEASE)
L8          792 S L6 AND L7
L9            1 S L5 AND L8

=> s l3 and l8
L10           2 L3 AND L8

=> s l10 not l9
L11           1 L10 NOT L9

=> d l11 1 ibib abs

L11  ANSWER 1 OF 1  EMBASE  COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER:   96170609  EMBASE
DOCUMENT NUMBER:    1996170609
TITLE:              Lentinan regulates the local inflammatory cellular
reaction
                    at tumor tissues - Its relation with antitumor effects.
AUTHOR:             Hamuro J.
CORPORATE SOURCE:   Ajinomoto Co., Inc., Basic Research Institute, 1-1
                    Suzuki-cho,Kawasaki-ku, Kawasaki 210, Japan
SOURCE:             Biotherapy, (1996) 10/4 (581-588).
                    ISSN: 0914-2223  CODEN: BITPE
COUNTRY:            Japan
DOCUMENT TYPE:      Journal; General Review
FILE SEGMENT:       016     Cancer
                    026     Immunology, Serology and Transplantation
LANGUAGE:           Japanese
SUMMARY LANGUAGE:   English; Japanese
```

AB Either immunotherapy or chemotherapy requires anticachectic treatments to improve its therapeutic effects leading to life prolongation. Cachexia is mainly induced by oxidative local cellular inflammatory reactions at tumor tissues by production of PGE2, reactive oxygen intermediates and **cachectic**/immunosuppressive cytokines such as IL-6, IL-1, TNF and TGF-.beta.. To induce the efficient specific immunological responses to tumor antigens, it is necessary to induce cellular reactions at tumor tissues to break the dormant state (ignorance of tumor antigens by host immune systems). The induction of cellular reactions at tumor tissues is confronted frequently with the conversion of cellular reactions into oxidative inflammatory reactions via overactivation of **macrophages** (M.phi.) and neutrophils. Lentinan suppresses the conversion and maintain the redox state of M.phi. at the reduced state designated by the high content of the reduced form of **glutathione** (**GSH**). M.phi.s with the high content of **GSH** respond to TH1 cytokines to produce an increased amount of NO and a reduced amount of IL-6, whereas M.phi.s with decreased **GSH** content respond in a manner resulting in inverse effects. In the advanced stage of **cancer** patients, the oxidative M.phi.s are responsible for the induction of TH2 cytokines responses resulting in the induction of cachexia.

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(FILE 'HOME' ENTERED AT 14:53:22 ON 31 JAN 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, AGRICOLA' ENTERED AT 14:53:49 ON 31 JAN 2002

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L1        448179 S MACROPHAGE
L2        225702 S GLUTATHIONE OR GSH
L3          2653 S L1 (P) L2
L4         44743 S CYSTINE
L5            95 S L3 (P) L4
L6          1789 S CACHECTIC OR CHACHEXIA
L7       2386695 S CANCER OR DIABETES OR (GASTROINTESTINAL INFLAMMATORY
DISEASE)
L8           792 S L6 AND L7
L9             1 S L5 AND L8
L10            2 S L3 AND L8
L11            1 S L10 NOT L9

=> s (l3 or l5 ) and l7
L12          164 (L3 OR L5 ) AND L7

=> s l12 and l4
L13            7 L12 AND L4

=> duplicate remove l13
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L13
L14            4 DUPLICATE REMOVE L13 (3 DUPLICATES REMOVED)

=> s l14 not l10
L15            3 L14 NOT L10

=> d l15 1-3 ibib abs

L15  ANSWER 1 OF 3     MEDLINE
ACCESSION NUMBER:    97407640      MEDLINE
DOCUMENT NUMBER:     97407640    PubMed ID: 9264389
TITLE:               Increased cystine uptake capability associated
                     with malignant progression of Nb2 lymphoma cells.
AUTHOR:              Gout P W; Kang Y J; Buckley D J; Bruchovsky N; Buckley A R
CORPORATE SOURCE:    Department of Cancer Endocrinology, British Columbia
Cancer
                     Agency, Vancouver, Canada.
CONTRACT NUMBER:     DK44439 (NIDDK)
                     RR05407 (NCRR)
SOURCE:              LEUKEMIA, (1997 Aug) 11 (8) 1329-37.
                     Journal code: LEU; 8704895. ISSN: 0887-6924.
PUB. COUNTRY:        ENGLAND: United Kingdom
                     Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         199709
ENTRY DATE:          Entered STN: 19970916
                     Last Updated on STN: 20000303
                     Entered Medline: 19970904
AB   Analysis of rat, pre-T cell 'Nb2 lymphoma' sublines, manifesting
different
     degrees of malignant progression, can indicate phenotypic changes
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potentially useful as therapeutic targets. In this study, the prolactin (cytokine)-dependent Nb2-11 and autonomous Nb2-SFJCD1 sublines were compared for in vitro thiol growth requirements. Whereas Nb2-11 culture growth depended on 2-mercaptoethanol (2-ME; 33-100 microM), Nb2-SFJCD1 cells were 2-ME-independent. This difference stemmed from differential uptake of exogenous L-**cystine**, critically required for proliferation. Uptake of 35S-L-**cystine** (10 microCi/ml; 40 microM) showed Nb2-11 cells had low **cystine** uptake capability; 2-ME enhanced **cystine** uptake to growth-sustaining levels. Nb2-SFJCD1 cells did not require 2-ME due to intrinsic, 11-fold higher **cystine** uptake via the x(c)- **cystine**/glutamate transport system. In absence of 2-ME, monosodium glutamate abrogated Nb2-SFJCD1 proliferation by specifically inhibiting **cystine** uptake (85% at 10 mM). Elevated **glutathione** (**GSH**) levels were not essential for growth of either line as shown with L-buthionine-(S,R)-sulfoximine (0.1-4 mM) treatment. The cyst(e)ine requirement therefore did not primarily involve maintenance of normal **GSH** levels, reported critical for T lymphocyte replication. These and other results suggest increased **cystine** uptake capability constitutes another potential step in progression of T cell **cancers** which is not coupled to cytokine autonomy or metastatic ability development. The x(c)- transport system apparently provides a novel target for T cell **cancer** therapy. Its inhibition would suppress **cystine** uptake by certain progressed cells, and also interfere with **cystine** uptake, and subsequent cysteine release, by eg **macrophages**, thought to have a role in cysteine delivery to lymphoid cells.

L15 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:583141 CAPLUS
DOCUMENT NUMBER: 131:223492
TITLE: Immunomodulators for the treatment of immune diseases
INVENTOR(S): Hamuro, Junji; Murata, Yukie
PATENT ASSIGNEE(S): Ajinomoto Co., Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 20 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| JP 11246435 | A2 | 19990914 | JP 1998-308300 | 19981029 |
| EP 1004302 | A2 | 20000531 | EP 1999-107480 | 19990429 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| US 2001000784 | A1 | 20010503 | US 2000-731830 | 20001208 |

PRIORITY APPLN. INFO.: JP 1997-312727 A 19971029
JP 1998-308300 A 19981029
US 1998-181881 A2 19981029
US 1999-334647 A1 19990617

OTHER SOURCE(S): MARPAT 131:223492
AB This invention relates to a method for the treatment of immune diseases by oral administration of immunomodulators which change oxidative and reductive conditions of macrophages and monocytes. **Cystine**

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derivs. are effective for the improvement of conditions such as cachexia, **diabetes**, digestive tract inflammation, and **autoimmune inflammatory diseases**.

L15 ANSWER 3 OF 3 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1992:347942 BIOSIS
DOCUMENT NUMBER: BA94:40167
TITLE: DYSREGULATION OF PLASMA AMINO ACID LEVELS IN HIV-INFECTION AND **CANCER** AND ITS RELEVANCE FOR THE IMMUNE SYSTEM.
AUTHOR(S): DROEGE W; ECK H P; GMUENDER H; MIHM S
CORPORATE SOURCE: DIV. IMMUNOCHEM., INST. IMMUNOL. GENETICS, DEUTSCHES KREBSFORSCHUNGSZENTRUM, D-W-6900 HEIDELBERG, GER.
SOURCE: AMINO ACIDS (VIENNA), (1991) 1 (2), 193-198. CODEN: AACIE6.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB T cells have a weak membrane transport activity for **cystine** but strong transport activity for cysteine. Even moderate variations of the cysteine concentration affect T cell functions in spite of the high concentration of **cystine** in cultures with physiological amino acid concentrations. The IL-2 dependent DNA synthesis and the activation of cytotoxic T cells are positively regulated by cysteine, while the activity of the transcription factor NF.kappa.B and the production of IL-2 are stimulated by active oxygen species and inhibited by cysteine or **GSH**. **Macrophages**, in contrast to T cells, take up more **cystine** than they need and release the excess after intracellular reduction as cysteine into the extracellular space. This "cysteine pumping activity" of **macrophages** raises intracellular **GSH** levels and DNA synthesis of T cells in the vicinity. The difference between the **cystine** transport activities of T cells and **macrophages**, therefore, enables T cells to switch between prooxidant and antioxidant states. The "cysteine pump" favors selectively the antigen-specific T cells that are about to be stimulated by antigen-presenting **macrophages**. The capacity of **macrophages** to take up **cystine** and to release cysteine is inhibited, however, by elevated extracellular glutamate concentrations.

Elevated plasma glutamate levels have been found in several pathological conditions including **cancer** and HIV-infection. In HIV-infected patients, the hyperglutamataemia is aggravated by hypocystinaemia and hypocysteinaemia. Our studies, therefore, suggest that the cysteine supply is impaired in several pathological conditions with immunodeficiencies including AIDS. N-acetyl-cysteine (NAC) is a safe and well established drug that may be considered for the treatment of patients with HIV-infection.

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(FILE 'HOME' ENTERED AT 14:53:22 ON 31 JAN 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, AGRICOLA' ENTERED AT 14:53:49 ON 31 JAN 2002
L1 448179 S MACROPHAGE

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```
L2       225702 S GLUTATHIONE OR GSH
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DISEASE)
L8          792 S L6 AND L7
L9            1 S L5 AND L8
L10           2 S L3 AND L8
L11           1 S L10 NOT L9
L12         164 S (L3 OR L5 ) AND L7
L13           7 S L12 AND L4
L14           4 DUPLICATE REMOVE L13 (3 DUPLICATES REMOVED)
L15           3 S L14 NOT L10

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY     SESSION
FULL ESTIMATED COST                                   65.72       65.87

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY     SESSION
CA SUBSCRIBER PRICE                                   -1.24       -1.24

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